

## REMARKS

### Claim Status

Claims 184-201 are pending, with elected claims 184-186 presented for examination.

### General Comments

Applicant submits this RCE in an effort to clarify the cited literature, particularly the Timko reference (WO 00/67558), which is central to the remaining rejections. Specifically, confusion exists regarding whether Timko discloses tobacco plants with increased nicotine. See Final Office Action, page 2.

The PTO is understood to take the position that Timko discloses tobacco plants with increased nicotine. Office Action, page 2. Accordingly to the PTO, that is, “Timko *et al.* disclose conferring high levels of transcription of PMT (i.e. overexpression of PMT), and as a result, higher levels of nicotine (page 5, lines 8-12).” *Id.* Further, the PTO alleges that “Timko *et al.* compare low nicotine mutants with the engineered tobacco plants with transcripts encoding PMT, thus showing that increased nicotine plants were created...(pages 29-30).” *Id.*

Yet, although Timko discloses putrescine N-methyltransferase (PMT) coding sequences, there is no hint of overexpressing PMT to produce tobacco plants with increased nicotine levels. In fact, Timko neither teaches nor suggests producing increased nicotine plants generally, let alone plants that are increased-nicotine by virtue of overexpressing PMT.

Timko’s low nicotine mutants, to which the PTO refers, are just that: low nicotine mutants. As explained on pages 29 and 30 of the reference, Timko compared transcript levels between a low-alkaloid tobacco Burley 21 mutant and wild-type Burley 21. This comparison was performed to determine the effects of topping on alkaloid levels. Thus, Timko reports that topping induced PMT in the wild-type only; the mutant did not respond to topping. *Id.*

It is apparent, therefore, that Timko did not genetically engineer or overexpress any sequence to produce transgenic tobacco plants with increased nicotine. This is not surprising

since it was applicant, not the cited art, who determined that tar-to-nicotine ratios could be manipulated by genetically increasing nicotine levels. Indeed, applicant's contribution to the art is underscored by the very fact that Timko says nothing about genetically engineering to increase nicotine levels for any purpose, let alone as a means for manipulating tar- to-nicotine ratio, as presently recited.

### **Rejections under 35 U.S.C. § 103**

#### **A. Claims 184 and 185**

Claims 184 and 185 remain rejected over Perkins *et al.* (USPN 3,861,400) in view of Newton Jr. *et al.* (USPN 3,957,060), Timko (WO 00/67558), Russell (Nicotine and Public Health, 2000), and Gibson (USPN 3,878,850). Office Action, pages 4-6.

Specifically, the PTO alleges that “Perkins *et al.* disclose cigarettes with a tar to nicotine ratio between 3 and 8 and that the pH of the smoking material should be kept below approximately 6.5.” *Id.* at page 4. Yet, the PTO admits that “Perkins *et al.* do not disclose that the tar to nicotine ratio was measured by FTC or ISO methods, the use of transgenic *Nicotiana tabacum* to supply nicotine, or that the pH of the cigarette smoke produced has a pH of 6.5 or lower.” *Id.* at page 5. To remedy these admitted deficiencies, the PTO relies on Timko, as “Timko *et al.* teach the engineering of *Nicotiana tabacum* to produce higher levels of nicotine using a heterologous coding sequence to boost levels of PMT which is an enzyme whose presence is a rate limiting step in supplying nicotine synthesis in tobacco.” *Id.* The PTO cites Gibson for disclosing “a choky flavor is associated with an alkaline trend in pH of smoke” and Russell for disclosing specific tar to nicotine ratios. *Id.* at page 6.

Pursuant to this reasoning, the PTO alleges that it “would have been obvious to make the cigarette of Perkins *et al.* with the tobacco of Timko *et al.*, and adjust the pH to lower than 6.5 by the methods and materials of Gibson *et al.* if the pH of the smoke produced was alkaline in nature or produced “choky” flavor.” *Id.* at page 6. Applicants respectfully traverse the grounds for this rejection.

In order to validate a conclusion that a claim would have been obvious, the PTO must show that all recited elements of the claim were evidenced in the art. Further, the PTO must demonstrate that one of ordinary skill in the art could have combined the elements in the manner claimed, via known methodology, with no change in the respective function(s) of the elements and with the resultant combination yielding nothing more than predictable results. *KSR v. Teleflex*, 127 S. Ct. 1727, 1739 (2007).

If any of these requirements does not pertain, then the PTO is barred from concluding that the claim in question would have been obvious. Such is the case here because no reasonable combination of the references could have led the skilled artisan to a cigarette comprising a portion of an increased-nicotine transgenic *Nicotiana tabacum* plant, where the cigarette is characterized by (i) a tar-to-nicotine yield ratio of between about 3 and about 8, as measured by the FTC or ISO method, and (ii) cigarette smoke having a pH of about 6.5 or lower.

Applicants and PTO agree that the primary reference, Perkins, discloses adding exogenous nicotine to increase the nicotine content of a smoking product. That is, Perkins teaches adding nicotine pectinate or nicotine alginate to reconstituted tobacco or a non-tobacco substitute material to increase the nicotine content of the resultant smoking product. In sharp contrast, the instant tobacco itself has increased nicotine content without adding exogenous nicotine. Through genetic engineering, therefore, applicants remove the need for adding external nicotine sources to tobacco thereby facilitating cigarettes with increased nicotine and desirable tar-to-nicotine ratios.

As discussed above, the PTO understands Timko to produce increased nicotine tobacco plants. Office Action, page 2. As explained above under “General Comments,” however, Timko does not genetically engineer or overexpress any sequence to produce transgenic tobacco plants with increased nicotine. Timko simply compared transcript levels between a low-alkaloid tobacco Burley 21 mutant and wild-type Burley 21, with no suggesting of a genetic-engineering manipulation or overexpress of any kind.

Because Timko thus neither teaches nor suggests a transgenic, increased-nicotine *Nicotiana* plant, one could not have merely “substitute[d]” Perkin’s tobacco cigarettes with Timko’s tobacco, thereby to produce a product having increased nicotine, as presently claimed. For this reason alone, the rejection is improper and should be withdrawn.

Because Timko does not provide increased nicotine tobacco, as the PTO posits, it appears the PTO bases its rejection on improper hindsight reconstruction. That is, the PTO improperly harnesses applicants’ own specification to “reconstruct” applicants’ own claimed cigarette. Such hindsight reconstruction can not be used for establishing obviousness, as the Federal Circuit has made clear that “Obviousness is determined as a matter of foresight, not hindsight.” *KSR* at 421. Thus, for this reason alone, the rejection is improper and should be withdrawn.

In the absence of any evidence of record to the contrary, moreover, the PTO has not established that Perkin’s tobacco product is essentially equivalent and thus amenable to substitution with Timko’s tobacco. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicants’ disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *See* MPEP § 2144.06. Here, the PTO provides neither evidence nor explanation for establishing any equivalency between Perkin’s tobacco product and Timko’s tobacco, let alone any reason for such substitution.

Even if the PTO had proffered rationale for equivalency between Perkin’s tobacco product and Timko’s tobacco, such rationale would surely fall short because Timko does not disclose tobacco plants overexpressing PMT with increased nicotine. That is, while Timko discloses PMT coding sequences, no where does Timko disclose overexpressing PMT to produce tobacco plants with increased nicotine levels. Thus, and contrary to the PTO’s position, Timko does not disclose tobacco plants with increased nicotine.

Accordingly, no permutation of the cited art teaches or suggests genetically engineering tobacco to produce smoking articles having increased nicotine and decreased tar-

to-nicotine ratio. Because the cited references therefore do not render the present claims obvious, the rejection should be withdrawn.

#### **B. Claim 186**

Claim 186 remains rejected over Perkins *et al.* (USPN 3,861,400) in view of Newton Jr. *et al.* (USPN 3,957,060), Timko (WO 00/67558), Russell (Nicotine and Public Health, 2000), Gibson (USPN 3,878,850), as applied to claim 184 above, further in view of Conkling *et al.* (USPN 6,423,520). Office Action, pages 6 and 7.

In particular, the PTO alleges “Timko *et al.* discloses uses genetic engineering to increase expression or production of PMT, but do not disclose up-regulating quinolate phosphoribosyl transferase (QPT or QPRTase).” *Id.* at page 6. The PTO relies on Conkling for “creating a transgenic *Nicotiana* having increased QPRT expression when compared to altering the expression of QPRTase by using complimentary nucleic acid sequences encoding a segment of QPRTase (abstract).” *Id.* In so doing, the PTO alleges that “it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the methods of Timko *et al.* and Conkling *et al.* to increase production of the two different, known, rate limiting enzymes in the production of nicotine, and thus increasing nicotine production in transgenic plants that result from genetic manipulation.” *Id.* at page 7.

Applicant traverses the grounds for this rejection. As discussed above, no reasonable combination of the primary references suggests genetically engineering tobacco as an approach to producing a cigarette with increased nicotine and a desirable tar-to-nicotine ratio. That is, because none of the cited references discloses increased nicotine plants, the primary references cannot render the present claims obvious, within the meaning of Section 103.

Conkling does not remedy these admitted deficiencies because Conkling likewise fails to suggest a cigarette made from genetically engineered tobacco with increased nicotine content. Accordingly, no permutation of the cited references could render the present claims obvious under Section 103, and the rejection therefore should be withdrawn.

### CONCLUSION

Applicant submits that this application is in condition for allowance and they request an early indication to this effect. Examiner Felton is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

Respectfully submitted,

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